Osmotic Drug Delivery Systems for Poorly Soluble Drugs

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Introduction

The pharmaceutical industry over the past decade has faced continuing challenges in bringing new chemical entities (NCEs) to market. In addition, the cost of developing NCEs keeps rising, and today stands at more than US$800 M per NCE. Drug discovery research has to continue to find new therapies for the prevention and treatment of existing and new diseases. There is, however, a valuable role being played by drug delivery systems in providing optimised products for existing drugs in terms of either enhanced or improved presentation of the drug to the systemic circulation.

Drug Delivery

The role of drug delivery today is to take a therapeutically effective molecule with sub-optimal physicochemical and/or physiological properties and develop an optimised product that will still be therapeutically effective but with added benefits (see *Table 1*). This is accomplished using the concepts of bioavailability enhancement and controlled release. For NCEs with sub-optimal properties, drug delivery approaches could provide a cheaper and faster route to the market than going back to the drawing board to design an analog with just the right physicochemical properties.

Controlled- or modified-release drug products have been successfully marketed for many years. These products (see *Table 2*) include dosage forms for oral and transdermal administration, as well as injectable and implantable systems.

Benefits of Drug Delivery
Decreased dosing frequency
Reduced peak-to-trough ratio of drug in systemic circulation
Reduced rate of rise of drug concentration in blood
Sustained and consistent blood levels within the therapeutic window
Enhanced bioavailability
Reduced interpatient variability
Customised delivery profiles
Reduced side-effects
Improved patient compliance

Table 1 – Benefits of drug delivery.

Name	Marketer	Dosage Form	Indication
Carbatrol	Shire US	Oral Capsule	Epilepsy
Glucotrol XL	Pfizer	Oral Tablet	Hyperglycaemia
Adderall XR	Shire US	Oral Capsule	ADHD
Procardia XL	Pfizer	Oral Tablet	Angina/Hypertension
Ortho Evra	Ortho-McNeil	Transdermal Patch	Contraceptive
Duragesic	Janssen	Transdermal Patch	Chronic Pain
Climara	Berlex	Transdermal Patch	Oestrogen replacement
Catapres-TTS	Boehringer Ingelheim	Transdermal Patch	Hypertension
Lupron Depot	TAP	Intramuscular Injection	Endometriosis
Doxil	Ortho Biotech	Intravenous Infusion	Ovarian cancer and Kaposi's sarcoma
Viadur	Bayer	Subcutaneous Implant	Advanced prostate cancer

Table 2 – Examples of marketed modified release products (Anon, 2004).

Oral Drug Delivery

For most drug products, the oral route remains the predominant and most acceptable mode of administration. Certain molecules may have low oral bioavailability because of solubility or permeability limitations. At **Shire Laboratories**, such molecules are run through a preformulation screen (ProScreen®) to identify the challenge to oral bioavailability. The next step of the screening effort (OptiScreen®) is to identify approaches to overcome the challenge/s determined earlier. The solution to the challenge is then incorporated into the formulation development effort using one of the available oral technologies.

Development of an extended-release dosage form also requires the drug to have reasonable absorption throughout the length of the GI tract. Determination of whether the drug may have a region of absorption issue can be done either in an animal pharmacokinetic study or evaluated in a Phase I clinical study.

Many companies have developed expertise with oral solid drug delivery technologies (see *Table 3*), which include multiparticulates in capsule, matrix tablet, and osmotic tablet. Of these, osmotic tablet technology is the most complex and one that can deliver a zero-order or time-independent release of drug from the dosage form.

Company	Matrix	Multiparticulate	Osmotic
ALZA			●
Elan	●	●	
Eurand	●	●	
Ethypharm	●	●	
Penwest	●		
Shire Labs	Solutrol	Microtrol	EnSoTrol
Skyepharma	●		

Table 3 – Oral solid controlled release capabilities.

Osmotic Drug Delivery Systems

Development of osmotic drug delivery systems was pioneered by **ALZA**. These systems use the principle of osmosis to deliver drugs from the tablet dosage form in a controlled manner, typically in a zero-order profile. The drug release from such optimised systems is independent of GI motility and GI pH.

Elementary Osmotic Pump (EOP)

The simplest of such systems is the EOP shown in Figure 1. The physical principles and equations determining the performance of such a system have been presented previously by Theeuwes (1975, 1985). The EOP consists of a single layer tablet core containing a water-soluble drug with or without other osmotic agents. A semi-permeable membrane surrounds the tablet core. The membrane is drilled with a delivery orifice. When such a system is swallowed, water from the GI tract enters through the membrane in to the core, the drug dissolves, and the drug solution is pumped out through the exit orifice. The EOP, however, is not suitable for delivering poorly soluble drug moieties.

Poorly Soluble Drugs and Osmotic Drug Delivery

OROS® Push-Pull™

The OROS Push-Pull system was developed at ALZA to overcome the challenge of delivering poorly soluble drugs using osmotic drug delivery. The Push-Pull system (*Figure 2*) comprises a bilayer or trilayer tablet core consisting of one push layer and one or more drug layers. The drug layer contains the poorly soluble drug, osmotic agents and

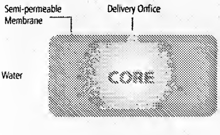

Figure 1 – Elementary osmotic pump.

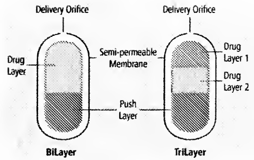

Figure 2 – OROS® Push-Pull.

suspending agents. The push layer contains among other things, osmotic agents and water-swellable polymers. A semi-permeable membrane surrounds the tablet core, as in the EOP system, and an orifice drilled in it on the drug layer side.

Upon ingestion of the Push-Pull system, water is drawn in to the drug layer, where the drug is suspended in the fluid. The push layer expands when water is drawn in due to the presence of water-swellable polymers. The expanding push layer delivers the drug suspension through the exit orifice at a controlled rate in the GI tract. The drug is then required to be dissolved in the GI fluids before being absorbed into the systemic circulation. Products commercialised using the Push-Pull system include Glucotrol XL® and Procardia XL® both composed of bilayer tablet cores, and Concerta® composed of a trilayer tablet core. Interpatient variability in plasma profiles can be expected because the drug is delivered in suspension form with a remaining dissolution step.

L-OROS™

To overcome the drug solubility issue, ALZA developed the L-OROS system (*Figure 3*) where a liquid softgel product containing drug in a dissolved state is initially manufactured and then coated with a barrier membrane, then an osmotic push layer and then a semi-permeable membrane drilled with an exit orifice.

EnSoTrol®

Shire Laboratories uses an integrated approach to drug delivery focusing on identification of barriers to oral drug delivery (ProScreen), screening of enhancers to overcome

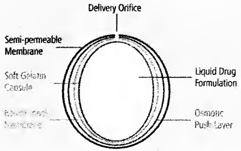

Figure 3 – L-OROS™.

- Significantly Increased Nifedipine Solubility in Aqueous Solution (1000X)
- Response Surface Diagram for Nifedipine Solubility

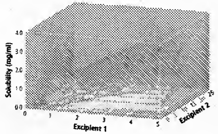

Figure 4 – OptiScreen® solubility enhancement.

the identified barrier/s (OptiScreen), and incorporation of the identified enhancers into controlled-release technologies to create an optimised dosage form. Solubility enhancements of an order of magnitude or more can be achieved, as shown for nifedipine in Figure 4. This approach was utilised to build a patented (Rudnic *et al.*, 2000) osmotic drug delivery platform, called EnSoTrol, for poorly soluble compounds. The EnSoTrol system consists of a single layer tablet core surrounded by a semi-permeable membrane. The membrane is drilled with an exit orifice. The tablet core includes the drug, osmotic agent, wicking agent and solubility enhancer/s to help dissolve the drug. A schematic of this system is shown in Figure 5.

When the EnSoTrol tablet is swallowed, water enters the core through the membrane. The presence of the solubility enhancer in the core helps dissolve the drug and the drug solution is delivered through the exit orifice to the GI lumen where it can be absorbed into the systemic circulation. The interpatient variability in plasma concentrations from the EnSoTrol system can be expected to be better because the poorly soluble compound is delivered from this tablet in a dissolved state.

Robust manufacturing processes are important with any technology, but more so with controlled delivery systems. For example, a rate-controlling membrane where the components are non-uniformly distributed (*Figure 6*) will perform variably versus a coating process that produces a homogenous membrane (*Figure 7*) batch to batch. Figure 8 shows an irregular orifice drilled using non-optimised laser parameters. When these parameters are optimised, the laser can consistently drill a uniform exit orifice (*Figure 9*) to improve the overall performance of the technology.

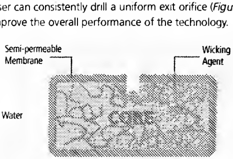

Figure 5 – EnSoTrol®.

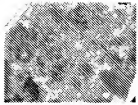

Figure 6 – Non-uniform membrane.

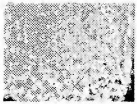

Figure 7 – Uniform membrane.

Figure 8 – Irregular delivery orifice.

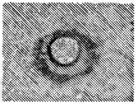

Figure 9 – Uniform delivery orifice.

To test the EnSoTrol technology, a Phase I clinical study was conducted in a group of 18 subjects comparing 60 mg nifedipine in an EnSoTrol formulation with Procardia XL containing 60 mg nifedipine in an OROS Push-Pull system. The mean plasma profiles from the two products are shown in Figure 10. A similar study was conducted with 10 mg glipizide XR formulation in EnSoTrol technology and compared with 10 mg Glucotrol XL containing 10 mg glipizide in an OROS Push-Pull system. The mean plasma profiles from the glipizide study are presented in Figure 11. As can be seen from the data, the two technologies produce similar mean plasma concentration profiles.

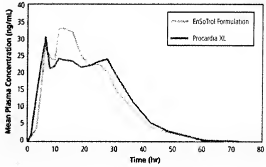

Figure 10 – Nifedipine XR Phase I study.

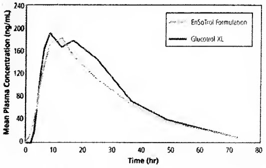

Figure 11 – Glipizide XR Phase I study.

Conclusion

Osmotic technologies produce a slightly higher cost of goods than matrix tablets or multiparticulates in capsule dosage form. However, the cost is worth the value provided in terms of the time-independent extended-release profiles that can translate into optimised *in vivo* profiles for short half-life drugs.

Drug delivery, in general, will continue to see significant growth in the pharmaceutical industry. Incorporation of drug delivery concepts, such as bioavailability enhancement and controlled release, into the development of NCEs is the next logical step.

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